Magnetization Transfer Imaging and Volume changes detected by MRI in first-episode schizophrenia

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Introduction

There is increasing evidence of structural brain imaging abnormalities in patients during their 'first-episode' of schizophrenia [1]. A systematic review and meta-analysis by Steen et al [1] suggested that whole brain volume is reduced in first-episode schizophrenia, although average volumetric changes are close to the limit of detection by MRI methods. Importantly, these volume losses do not appear to represent a specific pathological process as *post mortem* studies of schizophrenia do not demonstrate a clear neuropathological phenotype [2], or classic neurodegenerative changes [3;4;5]. Structural MRI is also non-specific in neuropathological terms as it is only able to detect abnormalities when they lead to volume loss. This stresses the need for novel approaches using MRI in the search for subtle pathology in first-episode schizophrenia, such as magnetization transfer imaging (MTI), which can detect abnormalities in the absence of volume loss. In this study we search for MTR and volume differences in first-episode schizophrenia using the largest subject sample to date, in an attempt to expand previous findings [6].

Methods

SUBJECTS: Forty eight patients (33 males and 15 females) were included in the study. Thirty eight had a final diagnosis of schizophrenia and ten of schizoaffective disorder (3 bipolar, 7 depressed subtypes). All patients were receiving antipsychotic medication (47 patients received second generation antipsychotics, 1 patient first-generation) and 7 were receiving antidepressant medication, and the average duration of treatment prior to scanning was 77 days (range 9 - 186 days). Forty seven healthy subjects (27 males and 20 females) served as controls. MRI: MRI was performed with a GE Signa 1.5 Tesla scanner (General Electric, Milwaukee, WI, USA), and the imaging protocol included the following sequences : 1) inversion recovery 3D spoiled gradient-recalled (IR-SPGR) echo sequence (TE=5 ms, TR=14ms matrix=256x128, field of view=31x16 cm^2, slice thickness=1.2mm, NEX=1, flip angle 20º, inversion time 450ms, 156 contiguous axial slices); 2) 3D MT- SPGR (TE=5 ms, matrix=256x128, field of view=31x16 cm^2, slice thickness=1.2mm, TR=22 ms, MT pulse flip angle=10º NEX=1), collecting 2 volumes, with and without MT-saturation, designed to match the IR SPGR in terms of FOV and resolution. POST-PROCESSING: First the two volumes from the MT-SPGR sequence were co-registered using FLIRT (http://www.fmrib.ox.ac.uk/fsl/), and MTR maps were then calculated on a pixel-by-pixel basis. The following steps were performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK), integrating the so-called "optimised VBM" approach [7] with matched steps performed on the MTR maps. For every subject, the MTR map was co-registered with the 3D IR-SPGR. Next, the 3D IR-SPGR underwent segmentation and normalisation as described by Good et al [7], and the same normalisation parameters were retrospectively applied to the MTR maps. Maps of grey and white matter density were then "modulated" (i.e. multiplied by the jacobian of the non-linear normalisation step to yield maps of grey and white matter volume). Finally, the normalised maps of whole-brain MTR, grey matter and white matter volume were smoothed with a 12 mm Gaussian kernel. STATISTICS: Group comparisons of grey matter, white matter and whole-brain MTR, testing for relative increases and decreases in gray matter, white matter and MTR were made using one sided t statistics and then corrected for multiple comparisons using a family-wise error correction at $p<(0.05)$. Post-hoc association between these quantities and clinical scores were evaluated by extracting the mean cluster MTR/Grey matter volume/white matter volume (for every cluster that was found to be different between groups) and correlating it against positive, negative and disorganization symptoms using Pearson's correlation.

Results

The MTR was found to be reduced ($p<0.05$, family-wise error corrected for multiple comparisons) in patients in the superior frontal gyrus, bilaterally, in the right fusiform gyrus, in the right enntorhinal cortex, in the right dentate gyrus and in the left inferior rostral/cingulate gyrus. Local grey matter loss was seen in the middle temporal gyrus, bilaterally, in the right insula and frontal operculum, and in the right superior temporal gyrus. An increase in regional grey matter was seen in patients in the region of the superior frontal gyri in both left and right hemispheres and a small region in the right superior temporal gyrus. Finally, there was a loss of white matter in the right hemisphere bordering the insular gyrus, middle and superior temporal gyrus region and the left temporal subgyral and insula region. These areas are shown in Fig 1. MTR of the medial temporal area was associated with positive symptoms, while MTR of the superior frontal gyrus was associated with disease duration.

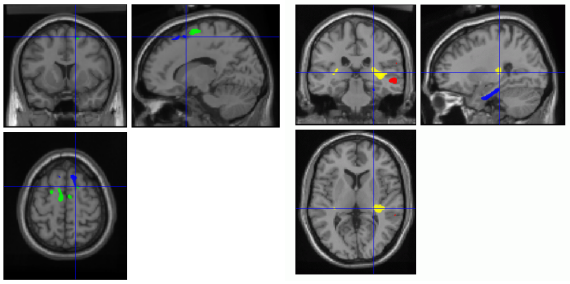

Fig 1. Areas of significantly reduced MTR (blue), significantly reduced grey matter volume (red), significantly increased grey matter volume (green) and significantly reduced white matter volume (yellow) in patients compared to controls.

Discussion

The results of this study suggest that MTR and volume abnormalities detected in patients compared to healthy controls reflect different underlying processes or different stages of a process in the illness as there was little overlap between grey/white matter volume and MTR differences between patients and controls. The MTR reductions seen in the patient group relative to the controls are in areas that have been previously implicated in the pathology of schizophrenia and also associated with clinical manifestations of the illness. Our study demonstrates that MTI is a useful tool to study the pathological processes in schizophrenia and suggests that pathological changes are present early in the disease and they are possibly associated with clinical dysfunction.

References

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